to interpret physiologically. The blood is a tissue, and histamine held inactive in its cells need have no different functional significance from that locked up in the cells of solid tissues. Code's (1937) work in my laboratory seemed, at the stage which it reached, to be pointing to the eosinophil cells as the source of most at least of the histamine extractable from normal blood; and, though it is also true that the abundant layer of platelets obtainable from citrated rabbit's blood seems to be the rich source in that species, I venture to suggest that a more critical haematology might throw light on the still rather curious anomaly that rabbit's whole blood yields so much more histamine than that of other common species. Another point which would, I suspect, repay further investigation is that of the possibility of the formation of histamine from proteins by hydrolysis, whether by enzymes or by heating with acids (cf. Abel and Kubota, 1919). I believe that it would be useful to have more definite evidence on the extent to which solutions containing "incoagulable" protein products can be heated with acid with a certainty that the histamine found in the product will be only that which was preformed in the original blood or other material.

4. Lastly, it seems to me that it might have an important bearing on our conception of the proper and safe use of the antihistamines if the evidence for the concern of histamine in the vasodilatation of normal functional activity were clearer and more consistent. I raised the question of this as a possibility in a lecture in 1919, pointing out how the relaxation of capillary tone by histamine would make it the ideal agent of a fine adjustment of the circulation to local metabolic needs if we had evidence that it existed in the tissue cells and that it was liberated by their normal activity. We have evidence of its presence now, but the evidence produced by Anrep and his colleagues for its liberation from active muscle still lacks confirmation. I need hardly point out that failure to detect an increase of it in the venous blood does not of necessity exclude the possibility of its local liberation and local action. It might, however, suggest the possibility that in relation to antihistamines it would behave more like "intrinsic" than "extrinsic" histamine. In any case, I suggest that further attempts to settle the matter, perhaps by experiments under conditions not so close to those of natural circulation, might provide useful information, and that clear evidence on this point might give valuable warning or reassurance concerning the use of the antihistamines in practice.

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CAFFEINE AND GASTRIC SECRETION

BY

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The effects of caffeine on gastric secretion have recently been investigated in animals and in man by Roth and Ivy (1944a, 1944b, 1944c) and by Merendino *et al.* (1945). It has been shown that, although there is a wide variation in sensitivity between species, caffeine stimulates gastric secretion in man, cat, guinea-pig, and dog. Man is relatively sensitive to this action of caffeine, while the dog is rather resistant. The effect is probably exerted directly on the parietal cells.

Roth and Ivy (1944a) showed that the intravenous injection of 65–125 mg. of caffeine into cats anaesthetized with chloroform provokes a secretion of acid gastric juice for about 45 minutes. Later they reported (Roth and Ivy, 1944c) that caffeine and histamine act synergistically in stimulating gastric secretion in the cat. The effect was considerable, and in one animal a previously ineffective dose of histamine stimulated secretion of highly acid juice after injection of caffeine. The doses of caffeine used were themselves large enough to cause a secretion of acid gastric juice, and it was desirable to determine whether the effect of histamine was potentiated by smaller doses of caffeine which did not stimulate gastric secretion. This was particularly necessary, since doses of 125 mg. of caffeine are bordering on the toxic for the cat, and attempts to repeat the experiments of Roth and Ivy often resulted in early death of the animal. At the same time theobromine and theophylline have been compared with caffeine in respect of this relation to histamine.

Methods

The cat, anaesthetized with sodium pentobarbitone intraperitoneally, was prepared for continuous drainage of gastric juice by Roth and Ivy's (1944a) modification of Lim's (1923) method. Ligatures were tied around the cardia and duodenum and a cannula was inserted into the stomach through the pylorus (see Wood, 1948). Juice was collected in graduated centrifuge tubes, and the free and total acid was estimated by titration with N/50 sodium hydroxide, using thymol blue as indicator for both endpoints.

One hour after the completion of the preparation, secretion being basal (less than 0.05 ml. in 10 minutes), histamine acid phosphate was injected subcutaneously in a dose equivalent to 0.27–0.65 mg. of histamine (about 0.18 mg. per kg. of body weight). The resultant secretion of juice was measured at intervals of 10 minutes until the basal level of secretion returned.

The particular xanthine compound was then slowly injected intravenously over a period of two to five minutes. Solutions (1 or 2%) of caffeine sodium benzoate, theobromine sodium salicylate, and theophylline sodium acetate were used containing respectively about 1/2, 1/2, and 5/9 of caffeine, theobromine, and theophylline (w/w). Doses of caffeine were 10–20 mg. per kg. (20–75 mg. total dose), of theobromine 20 mg. per kg. (34–54 mg.), and of theophylline 20 mg. per kg. (42–62 mg.).

Two groups of experiments were done with caffeine. In one group of seven cats the second dose of histamine, the same as the first in any one cat, was injected 40–60 minutes after caffeine. This interval allowed enough time for any possible stimulant action of caffeine to pass off. Caffeine itself caused a significant increase in secretion in only three

of the seven cats. In another six animals the second dose of histamine was injected immediately after the caffeine. Collection of juice was continued until the basal level of secretion returned. The second dose of histamine was injected 40–60 minutes after theobromine or theophylline in all experiments with these substances.

Results

Caffeine.—Following the intravenous injection of 20 mg. of caffeine per kg. there was at first irregularity and some slowing of the heart and a transient fall of blood pressure. A temporary respiratory stimulation also occurred. Neither of these effects was so obvious after theophylline or theobromine; the blood pressure often rose about 10–15 mm. Hg after theobromine. Both the magnitude and duration of the histamine stimulation of gastric secretion were increased after caffeine (Table I). This was observed in all 13 experiments. In three of the seven cats where there was an interval of 40–60 minutes between the injections of caffeine and of histamine there was a mild stimulation of secretion due to the caffeine alone. Thus caffeine has a potentiating action which is still present 40–60 minutes after it has been injected. Since these doses of caffeine have only a slight, if any, secretory stimulant action, the two sets of results have been combined to obtain average figures from 13 animals. A typical graph of the secretory response to histamine before and after caffeine is shown in the Chart.

Theobromine and Theophylline.—Results with these two xanthine derivatives were much more variable than those with caffeine. The histamine effect was appreciably increased after theobromine in three out of six cats (Table II). In one of these (No. 90) free acid secretion due to histamine was increased from 1.2 to 36.25 ml. of N/50 HCl. In cat No. 93 theobromine had some stimulant effect itself, but there was no significant increase in the effect of histamine after theobromine. The smaller effect of histamine after theobromine in cat No. 89 cannot be attributed to the theobromine, since second doses of histamine often have less effect than the first dose. There was some

TABLE I.—*Secretion of gastric juice and free acid (in ml. N/50 HCl) due to histamine before and after intravenous injection of caffeine (10–20 mg./kg.)*

Cat No.	Secretion Due to								
	Histamine			Caffeine			Histamine after Caffeine		
	Juice (ml.)	Free Acid (ml.)	Duration (min.)	Juice (ml.)	Free Acid (ml.)	Duration (min.)	Juice (ml.)	Free Acid (ml.)	Duration (min.)
70*	0·35	0·0	40	—	—	—	4·0	15·7	60
71	2·65	4·75	70	—	—	—	2·95	11·05	90
72	0·95	0·6	40	—	—	—	2·05	7·15	70
73	1·6	1·8	80	—	—	—	5·85	23·0	80
74	1·55	3·6	60	—	—	—	4·15	15·0	60
75	1·5	0·0	60	—	—	—	4·85	5·6	110
76†	2·5	12·3	60	0·3	0·8	60	4·6	22·65	100
77	1·5	1·4	60	1·05	3·15	60	4·8	20·45	90
78	2·75	6·15	60	2·35	6·05	60	13·35	64·8	140
80	1·7	0·85	60	0·1	0·4	30	6·0	25·25	110
81	1·55	2·45	70	0·25	0·45	40	6·4	18·7	90
82	3·0	9·9	80	0·4	1·6	40	7·65	38·75	140
83	1·35	1·5	70	1·15	1·35	50	6·75	27·95	80
Average	1·8	3·5	62	0·8	2·0	49	5·7	22·8	94

* In cats Nos. 70–75 the second histamine dose was given subcutaneously immediately after caffeine.
† In cats Nos. 76–83 the second histamine dose was given subcutaneously 40–60 minutes after caffeine.

TABLE II.—*Secretion of juice and free acid (ml. N/50 HCl) in response to subcutaneous histamine before and after 20 mg. of theobromine per kg. intravenously.*

Cat No.	Secretion Due to								
	Histamine before Theobromine			Theobromine			Histamine after Theobromine		
	Juice (ml.)	Free Acid (ml.)	Duration (min.)	Juice (ml.)	Free Acid (ml.)	Duration (min.)	Juice (ml.)	Free Acid (ml.)	Duration (min.)
89	9·2	45·8	110	0·4	2·3	50	6·95	28·15	110
90	1·25	1·2	70	0·75	2·75	60	27·65	36·25	110
91	3·0	11·7	80	1·35	2·55	50	3·4	12·05	90
92	1·0	0·7	60	0·9	2·1	50	1·2	2·8	50
93	1·55	0·9	70	1·8	4·2	60	0·75	1·15	60
94	0·65	0·1	60	0·15	0	20	3·5	4·9	80
Average	2·8	10·1	75	0·9	2·3	48	7·2	14·2	83

TABLE III.—*Secretion of gastric juice and free acid (ml. N/50 HCl) in response to subcutaneous histamine before and after 20 mg. of theophylline per kg. intravenously.*

Cat No.	Secretion Due to								
	Histamine before Theophylline			Theophylline			Histamine after Theophylline		
	Juice (ml.)	Free Acid (ml.)	Duration (min.)	Juice (ml.)	Free Acid (ml.)	Duration (min.)	Juice (ml.)	Free Acid (ml.)	Duration (min.)
85	1·0	0·85	60	1·0	1·0	60	1·1	2·2	70
86	2·6	2·55	80	1·7	3·15	60	12·05	53·9	150
87*	2·15	4·65	100	0·3	0·7	50	0·15	0·25	40*
88	0·95	0·6	50	1·6	5·25	60	0·45	1·7	60
95	0·65	0·1	50	0·25	0·1	40	0·5	0·15	60
96	1·1	1·05	60	0·65	0·8	50	0·8	0	60
Average	1·4	1·6	67	0·9	1·8	53	2·5	9·7	73

* This cat died 40 minutes after theophylline.

secretory response after theophylline in two, or possibly three, out of six animals (Table III). In one of these (No. 86) the histamine effect was very greatly increased after theophylline, there being five-fold and twenty-fold increases respectively in the volume of juice and free acid secreted. In this animal theophylline itself had a stimulant effect on secretion. There was a possible potentiation in cat No. 85.

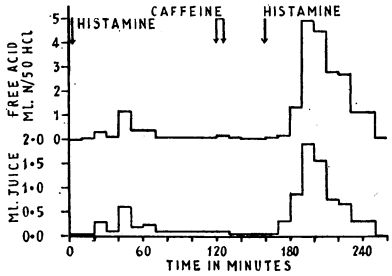

Chart showing the effect of histamine (0.35 mg. subcutaneously) on gastric secretion before and after a dose of caffeine (20 mg. per kg.) which did not stimulate secretion. Juice measured at intervals of 10 minutes (cat No. 81, weight 2 kg.).

The effect of histamine was less consistently altered after theobromine or theophylline than after caffeine, but occasionally there was a considerable increase.

Controls.—In control experiments repeated injections of a dose of histamine at intervals of one or two hours never gave an increasing response. Indeed, as Roth and Ivy (1944c) and others have indicated, there was a tendency towards a reduction in the secretory response to successive doses of histamine. Thus an increased effect of histamine after caffeine, etc., may be fairly attributed to the xanthine compound, but a reduction in the effect of histamine as in cats Nos. 87 and 89 is probably not due to the xanthine compound. Inspection of the gastric mucosa at the end of the experiment confirmed the findings of Roth and Ivy (1945). There was obvious hyperaemia and engorgement of the mucosa, particularly in those animals treated with caffeine. No quantitative estimate of the change was made, but it appeared much less after theophylline or theobromine. No similar effect was observed in the mucosa of any cat after repeated histamine injections or after continuous histamine infusion for several hours.

Discussion

Roth and Ivy showed that caffeine stimulates gastric secretion in the cat and also acts synergistically with histamine. They suggest that "the stimulation of gastric secretion may not necessarily be attributed to the same property of caffeine which is responsible for the synergism," since the synergistic action persists when the stimulant action of caffeine is over. The present results, showing that in doses which have no stimulant action on gastric secretion caffeine can potentiate the effect of histamine, support the probability that some other mechanism is responsible. Roth and Ivy (1945) have suggested that persistently increased blood flow accompanying vasodilatation might be a factor. Their later observations on the vascularity of the mucosa after caffeine strengthened this view. Observations on ulcers induced by caffeine in cats led them to suggest the following sequence of events caused by caffeine in the gastric mucosa: "vasodilatation and engorgement, vascular stasis, local anoxia, increased capillary permeability, transudation, exudation, and decreased cell nutrition." The vascular and cellular changes due to caffeine may make the mucosa more susceptible to the proteolytic action of acid and pepsin secretion.

The present results with theobromine and theophylline are less consistent and convincing. There is evidence that theophylline, at least, is a more potent vasodilator than caffeine, and it might have been expected to be at least as active as caffeine in potentiating the secretory action of histamine. To that extent this affords some evidence that the effect on blood flow is not necessarily the cause of the potentiating effect of caffeine. It is known that caffeine increases the oxygen uptake of resting frog muscle and that this increase is sensitive to azide (Stannard, 1939). It may be that caffeine also has some effect on an intracellular enzyme system concerned in gastric secretion, and this may underlie the potentiating effect of caffeine on histamine-induced gastric secretion. Whatever the explanation of the observed effect, certain conclusions are permissible. Even if histamine is not intimately concerned in either the physiology or pathology of gastric secretion, then consumption of large amounts of caffeine-containing drinks may be a factor in peptic ulcer formation or perpetuation. If histamine is associated with normal gastric secretion or with ulcer formation then the danger of excess caffeine intake is increased. It is still not justifiable, as Roth and Ivy (1946) stress, to conclude from the experimental results in animals that caffeine can cause peptic ulceration in man. It is known, however, that after a caffeine test-meal secretion of acid gastric juice is greater and more prolonged in ulcer patients than in normals (Roth, Ivy, and Atkinson, 1944).

The present experiments in normal cats show that caffeine potentiates the action of histamine on gastric secretion, and that theobromine and theophylline can have a similar action in some animals. Our results support Roth and Ivy's (1944b) conclusion that ulcer patients should restrict their intake of beverages containing caffeine, and also suggest that it is desirable to limit their consumption of foods and drinks containing theobromine and theophylline. These substances should equally be avoided by the patient with hyperchlorhydria but no ulcer.

Summary

Caffeine injected intravenously in a dose which does not usually stimulate gastric secretion in the anaesthetized cat consistently potentiates the gastric stimulant action of histamine.

A similar but less consistent effect was observed after theobromine and after theophylline.

The significance of these findings is discussed in relation to the management of the patient with peptic ulcer.

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Mr. John Edwards, Parliamentary Secretary to the Ministry of Health, paid tribute to the work of insurance committees when he addressed members of the London Insurance Committee on July 1 at their last meeting. "I think the finest tribute to their work is the decision to base much of the new health service on the existing arrangements. Without the co-operation of insurance committees it would have been very difficult for executive councils to prepare for the new scheme. They have most generously assisted executive councils from the very beginning by making the services of their staff available and by placing their offices and equipment at the councils' disposal. Wherever possible the Minister has included insurance committee members among his appointments to executive councils. I am quite sure that their experience will help to guide the councils over the difficult transitional period and ensure the continuity of administration which we are anxious to maintain." London, he said, had faced a special task: "Not only have you the largest register in the country but you also have the largest number of doctors and chemists in contract with you. I understand that there are 1,675 doctors on your list and that the chemists in contract with you have some 1,200 shops. Indeed, the magnitude of everything in London is always a challenge to those responsible for administration—a challenge which your committee has always successfully accepted."